MODULATION OF IMMUNE RESPONSE AND METHODS BASED THEREON

MODULATION OF IMMUNE RESPONSE AND METHODS BASED THEREON

1. FIELD OF THE INVENTION

The present invention relates to methods for the prevention and/or treatment of cardiovascular and allergic diseases and disorders, methods for inhibiting the growth of, or reducing the volume of, a solid tumor, as well as methods for preventing progression to AIDS in an HIV-positive human, by administering a peptide derived from T-cell receptors, or a derivative of the peptide. The present invention also relates to peptides derived from T-cell receptors, and derivatives of such peptides, which are useful in such methods.

2. BACKGROUND OF THE INVENTION

The immune response is a complex and dynamic process initiated by infection, autoantigens, tumor-associated antigens and transplantation that involves antigen presenting cells (macrophages or dendritic cells), antigen-specific thymus-derived lymphocytes (T-cells) that can be further discriminated into helper or cytotoxic T-cells, and antibody forming cells of the B cell lineage. The helper T cells can be further differentiated into subsets termed Th1 that produce mostly interferon-γ (IFN-γ), or interleukin-2 (IL-2), and Th2 cells that produce mainly interleukin-4 (IL-4) or interleukin-5 (IL-5). The Th1 cells function predominantly in inflammatory reactions, where they recruit macrophages and other non-lymphoid cell types in the destruction of infectious agents. The Th2-type cells help principally in the production of antibodies through interactions with B cells, and this role predisposes to the development of asthma and allergic reactivity because of the generation of the reagenic antibody IgE (Wills-Karp, 1999, Ann. Rev. Immunol. 17:255-81).

The complex interactions among the distinct cell types are regulated by the secreted cytokines, and it is now recognized that functional balance between the two subsets of T-cells is important for normal immunity (Romagnani, 1997, Immunology Today 18: 263-266; Infante-Duarte et al., 1999, Immunopathol. 21:317-338). The definition of Th1 and Th2 helper T cells is an operational one based on expression of cytokines considered characteristic of the individual subsets, although non-lymphoid cells can produce certain essential cytokines. Often, both Th1 and Th2 responses are ongoing in particular infections, especially at later stages. Th1-type responses are generally protective against intracellular parasites; whereas extra cellular parasites are better counteracted by so-called Th0 T-cells producing both Th1 and Th2 cytokines, thus generating both cellular and humoral immunity. Optimal protection against metazoan parasites such as helminths is apparently conferred by Th2 responses. Th2-type responses favor HIV progression by allowing

↳ NO DATA!!!

enhanced HIV replication in $CD4^+$ T-cells, and a strong imbalance between Th1 and Th2-type cytokine production is observed in mice infected with defective leukemia virus, the so-called MAIDS model (Watson et al., 1995, J. Immunol. 155:2282-2291; U.S. Patent No. 5,911,990 to Marchalonis et al.).

Polarized or unbalanced allergen-specific Th2 responses are responsible for initial triggering of allergic inflammation in atopic subjects. In general, polarization of Th1/Th2 cytokine expression induced by interaction of the pathogen with the host can lead to situations destructive to the host; *i.e.*, the Th1-Th2 shift in MAIDS. However, correction of the imbalance can restore beneficial protection to the infected animal. Th1-dependent protection and Th2-mediated susceptibility is found in the response to the intracellular parasite *Leishmania*, and in leprosy, caused by *Mycobacterium leprae*.

Thus, it would be beneficial to have compositions and methods for maintaining proper immune system functioning, *i.e.*, proper amounts and ratios of cytokine production, in the presence of an underlying pathogenic condition. One molecule that provides for the proper functioning of the immune system and suppression of progression to AIDS in an immunodeficiency-type retrovirus-infected individual is described in U.S. Patent No. 5,911,990 to Marchalonis et al. The molecule is a peptide that is derived from the T cell-receptor and has the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1). This peptide was shown to suppress progression to AIDS and normalize aberrant Th1 and Th2 cytokine production in individuals infected with an immunodeficiency-type retrovirus.

Citation of a reference in this or in any section of the specification shall not be construed as an admission that such reference is prior art to the present invention.

3. SUMMARY OF THE INVENTION

The present invention is directed to a T-cell receptor (TCR)-derived peptide, or a derivative of the peptide, and methods for their use. The TCR-derived peptide of the present invention is selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID

NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15).

The present invention is also directed to a derivative of the foregoing peptides of SEQ ID NOS:1-15. Such derivative peptides include those in which one or more amino acid residue has been replaced by a similar amino acid, residue, or the corresponding D-isomer, or by a non-naturally occurring amino acid residue. Other derivative peptides include cyclic derivatives of the peptides and chemical derivatives of the peptides of SEQ ID NOS:1-15. Other derivatives also include dual peptides or multimer peptides consisting of the same or of different peptides of SEQ ID NOS:1-15, wherein the peptides are covalently linked to one another directly or through a spacer. Other derivatives include those peptides which have insertions or deletions relative to the peptides of SEQ ID NOS:1-15.

The present invention is also directed to pharmaceutical compositions comprising a peptide of the present invention, or a derivative thereof, and a pharmaceutically acceptable carrier. The pharmaceutical compositions are used, *e.g.*, as promoters of Th1 cytokine production and/or inhibitors of Th2 cytokine production in an individual animal, preferably a mammal, including a human.

The present invention is also directed to methods for the use of a T-cell receptor derived peptide, or a derivative thereof, to increase production of at least one Th1 cytokine and/or decrease production of at least one Th2 cytokine, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID

NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual, in an amount sufficient to increase production of at least one Th1 cytokine and/or decrease production of at least one Th2 cytokine.

The present invention is also directed to methods for increasing production of at least one Th1 cytokine or decreasing production of at least one Th2 cytokine in an individual free of infection with an immunodeficiency-type retrovirus comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual free of infection with an immunodeficiency-type retrovirus in an amount sufficient to increase production of at least one Th1 cytokine or decrease production of at least one Th2 cytokine.

The present invention is also directed to methods for the use of a peptide or a derivative thereof for the prevention of progression to, or delay the onset of, AIDS in an immunodeficiency-type retrovirus infected individual, *e.g.*, an HIV-infected human, comprising administering a peptide selected from the group consisting of peptides

comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an immunodeficiency-type retrovirus infected individual, in an amount sufficient to arrest the development of immune dysfunction or cytokine dysregulation, which allows such retrovirus infections to immunologically weaken the host, *i.e.*, to prevent progression to, or delay the onset of, AIDS.

The present invention also provides methods for reversing the deleterious effects of infection with an immunodeficiency-type retrovirus, *e.g.*, HIV, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID

NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual infected with an immunodeficiency-type retrovirus, in an amount sufficient to reverse the deleterious effects of immunodeficiency-type retrovirus infection.

Methods of suppressing progression to immune dysfunction and cytokine dysregulation caused by HIV infection in an individual are also provided in the present invention, said method comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual infected with HIV in an amount sufficient to suppress or delay progression to immune dysfunction and cytokine dysregulation.

Moreover, methods for preventing immunosuppression and cytokine dysregulation induced by infection with an immunodeficiency-type retrovirus are also provided in the present invention, said method comprising administering to an individual infected with an immunodeficiency-type retrovirus a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln

Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, in an amount sufficient to prevent immunosuppression and cytokine dysregulation induced by infection with an immunodeficiency-type retrovirus.

The present invention is also directed to methods for the prevention and/or treatment of a disease or disorder of the cardiovascular system, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual in need thereof, in an amount sufficient to prevent or treat a disease or disorder of the cardiovascular system.

Illustrative disease and disorders of the cardiovascular system which can be ameliorated, prevented or treated according to the present invention include, but are not

limited to, atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, thrombus formation, and retrovirus-induced cardiovascular dysfunction.

The present invention is also directed to methods for the prevention and/or treatment of an allergic disease or disorder characterized by increased IgE production, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual in need thereof, in an amount sufficient to prevent or treat an allergic disease or disorder in which the disease or disorder is characterized by increased IgE production.

Illustrative examples of such allergic diseases and disorders characterized by increased IgE production include, but are not limited to, allergy, asthma, delayed hypersensitivity, septic shock, and anaphylactic shock.

The present invention is also directed to methods for inhibiting the growth of a solid tumor or reducing the volume of a solid tumor, comprising administering a peptide selected from the group consisting of peptide comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser

Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual in need thereof, in an amount sufficient to inhibit the growth of, or reduce the volume of, the solid tumor.

Solid tumors include, but are not limited to sarcomas, carcinomas, lymphomas or other solid tumor cancers, such as germ line tumors and tumors of the central nervous system, including, but not limited to, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, glioma, pancreatic cancer, stomach cancer, liver cancer, colon cancer, and melanoma.

The present invention also provides methods for preventing immunosuppression or suppressing progression to immune dysfunction or cytokine dysregulation in an individual infected with a viral, fungal or bacterial infectious agent other than an immunodeficiency-type retrovirus, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly

Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, in an amount sufficient for preventing immunosuppression or suppressing progression to immune dysfunction or cytokine dysregulation in an individual infected with a viral, fungal or bacterial infectious agent other than an immunodeficiency-type retrovirus.

4. DETAILED DESCRIPTION OF THE INVENTION

4.1 PEPTIDE AND PEPTIDE DERIVATIVES

The peptides, peptide derivatives and pharmaceutical compositions of the present invention can increase production of at least one Th1 cytokine and/or decrease production of at least one Th2 cytokine, *e.g.*, in an individual, in cell culture. The peptides and compositions have anti-immune activity, *i.e.*, inhibitory effects against IgE production. The peptides and compositions also inhibit the progression to AIDS in an immunodeficiency-type retrovirus-infected individual, as well as the ability to inhibit the growth of a solid tumor or the ability to reduce the volume of a solid tumor. The peptides and compositions also can treat or prevent cardiovascular diseases or disorders. As used herein, treating or preventing a disease or disorder also encompasses ameliorating at least one symptom of such disease or disorder.

In certain embodiments, the term "purified" is used to indicate that the peptide or peptide derivative is substantially free of foreign components, such as bacterial proteins or cellular debris, with which it is normally associated as a part of its production. In a preferred embodiment, substantially free indicates that at least 75% of the foreign components have been removed. In more preferred embodiment, at least 95% of the foreign components have been removed. In other certain embodiments, "purified" indicates that the peptide or peptide derivative is 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% of the total protein of a composition.

As used herein, the term "peptide" refers to molecules having no more than 250 amino acids. In certain embodiments, the peptide has about 5 to about 200 amino acids. In other embodiments, the peptide has about 10 to about 100 amino acids. In certain preferred embodiments, the peptide has about 5 to about 25 amino acids. In yet more preferred embodiments, the peptide has about 5 to about 20 amino acids.

As used herein, the term "peptide derivative" includes cyclic peptides; peptides obtained by substitution of a natural amino acid residue by a similar amino acid, the corresponding D-stereomer, or by a non-natural amino acid residue; chemical derivatives of the peptides; dual peptides; and multimers of the peptides. The term also

includes those peptide that have a deletion or insertion relative to the amino acid sequence of SEQ ID NOS:1-15. For example, a derivative of the peptides of SEQ ID NOS:3-11 is in which the 5'-most leucine residue is not present.

The term "cyclic peptides" as used herein are cyclic derivatives of the peptides of SEQ ID NOS:1-15 to which two additional amino acid residues suitable for cyclization have been added, one at the carboxyl terminus and one at the amino terminus. Thus, the cyclic peptides contain either an intramolecular disulfide bond, *i.e.*, -S-S-, an intramolecular amide bond between the two added residues, *i.e.*, -CONH- or -NHCO- or intramolecular S-alkyl bonds, *i.e.*, -S-$(CH_2)_n$-CONH- or -NH-CO$(CH_2)_n$-S-, wherein n is 1 or 2. In a preferred embodiment, the peptide Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1) is derivatized by the incorporation of two terminal cysteine residues and cyclized through an intramolecular S-S bond between the two incorporated cysteine residues. In yet another preferred embodiment, the peptide Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val (SEQ ID NO:2) is derivatized by the incorporation of two terminal cysteine residues and cyclized through an intramolecular S-S bond between the two incorporated cysteine residues.

The cyclic derivatives containing an intramolecular disulfide bond may be prepared by conventional solid phase synthesis (Merrifield et al., 1982) while incorporating suitable S-protected cysteine or homocysteine residues at the positions selected for cyclization such as the amino and carboxyl termini (Sahm et al., 1996, J. Pharm. Pharmacol. 48(2):197). Following completion of the chain assembly, cyclization can be performed either by selective removal of the S- protecting groups with a consequent on-support oxidation of the two free corresponding SH-functions, to form S-S bonds, followed by conventional removal of the product from the support and appropriate purification procedure, or by removal of the peptide from the support along with complete side-chain deprotection, followed by oxidation of the free SH-functions in highly dilute aqueous solution.

The cyclic derivatives containing an intramolecular amide bond may be prepared by conventional solid phase synthesis while incorporating suitable amino and carboxyl side-chain protected amino acid derivatives at the positions selected for cyclization. The cyclic derivatives containing intramolecular -S-alkyl bonds can be prepared by conventional solid phase synthesis while incorporating an amino acid residue with a suitable amino-protected side chain, and a suitable S- protected cysteine or homocysteine residue at the positions selected for cyclization.

According to another embodiment, a peptide of the invention has one or more of the amino acid residues replaced by the corresponding D-amino acid residue. Thus

the peptide or peptide derivative of the invention may be all-L, all-D or a D,L- peptide. In another embodiment, an amino acid residue may be replaced by a non-natural amino acid residue provided that the charge of the peptide is not substantially changed. Examples of non-naturally occurring or derivatized non-naturally occurring amino acids include Nα-methyl amino acids, Cα-methyl amino acids, β-methyl amino acids and amino acid analogs in general such as, but not being limited to, β-alanine (β-Ala), norvaline (Nva), norleucine (Nle), 4-aminobutyric acid (γ-Abu), 2-aminoisobutyric acid (Aib), 6-aminohexanoic acid (ϵ-Ahx), ornithine (Orn), hydroxyproline (Hyp), sarcosine, citrulline, cysteic acid, and cyclohexylalanine. In yet anther embodiment of the present invention, one or more amino acid residues can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

A chemical derivative of a peptide of SEQ ID NOS:1-15 includes, but is not limited to, a derivative containing additional chemical moieties not normally a part of the peptide provided that the derivative retains a function of the peptide. Examples of such derivatives are: (a) N-acyl derivatives of the amino terminal or of another free amino group, wherein the acyl group may be either an alkanoyl group, *e.g.*, acetyl, hexanoyl, octanoyl; an aroyl group, *e.g.*, benzoyl, or a blocking group such as Fmoc (fluorenylmethyl-O-CO-), carbobenzoxy (benzyl-O-CO-), monomethoxysuccinyl, naphthyl-NH-CO-, acetylamino-caproyl, adamantyl-NH-CO-; (b) esters of the carboxyl terminal or of another free carboxyl or hydroxy groups; (c) amides of the carboxyl terminal or of another free carboxyl groups produced by reaction with ammonia or with a suitable amine; (d) glycosylated derivatives; (e) phosphorylated derivatives; (f) derivatives conjugated to lipophilic moieties, *e.g.*, caproyl, lauryl, stearoyl; and (g) derivatives conjugated to an antibody or other cellular ligands.

Also included among the chemical derivatives are those derivatives obtained by modification of the peptide bond -CO-NH-, for example, by (a) reduction to $-CH_2-NH-$; (b) alkylation to -CO-N (alkyl)-; (c) inversion to -NH-CO-.

A dual peptide according to the invention consists of two the same or different peptides of the invention covalently linked to one another or through a spacer such

as by a short stretch of alanine residues or by a putative site for proteolysis by cathepsin (see U.S. Patent No. 5,126,249 and European Patent No. 495,049 with respect to such sites). This will induce site-specific proteolysis of the preferred form into the two desired analogues. In one embodiment the dual peptide is Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:16).

Multimers according to the invention consist of polymer molecules formed from a number of the same or different peptides or derivatives thereof. The polymerization is carried out with a suitable polymerization agent, such as 0.1% glutaraldehyde (Audibert et al., 1981, Nature 289:593).

In one aspect of the invention, the peptide derivative is more resistant to proteolytic degradation than the corresponding nonderivatized peptide. For example, a peptide derivative having D-amino acid substitution(s) in place of a L-amino acid resists proteolytic cleavage when administered to a mammal. In another aspect of the invention, the peptide derivative has increased permeability across a cell membrane than the corresponding nonderivatized peptide, *e.g.*, those peptide derivatives having a lipophilic moiety coupled at the amino and/or carboxyl terminus. In yet another aspect, the peptide derivative has enhanced biological activity, *e.g.*, those peptide derivatives which are dualized or multimerized peptides.

The peptides or peptide derivatives of the present invention are obtained by any method of peptide synthesis known to those of skill in the art, including synthetic and recombinant techniques. For example, the peptides or peptide derivatives can be obtained by solid phase peptide synthesis, which, in brief, consists of coupling the carboxyl group of the C-terminal amino acid to a resin and successively adding N-alpha protected amino acids. The protecting groups may be any known in the art. Before each new amino acid is added to the growing chain, the protecting group of the previous amino acid added to the chain is removed. The coupling of amino acids to appropriate resins is described by Rivier et al., U.S. Patent No. 4,244,946. Such solid phase syntheses have been described, for example, by Merrifield, 1964, J. Am. Chem. Soc. 85:2149; Vale et al. 1981, Science 213:1394-1397; Marki et al., 1981 J. Am. Chem. Soc. 103:3178 and in U.S. Patent Nos. 4,305,872 and 4,316,891. In a preferred aspect, an automated peptide synthesizer is employed.

Purification of the synthesized peptides or peptide derivatives is carried out by standard methods including chromatography (e.g., ion exchange, affinity, and sizing column chromatography), centrifugation, differential solubility, hydrophobicity, or by any other standard technique for the purification of proteins. In a preferred embodiment, thin

layer chromatography is employed. In yet another preferred embodiment, high performance liquid chromatography (HPLC) under reverse phase conditions is employed to purify a peptide or peptide derivative of the present invention.

4.2 COMPOSITIONS OF AND METHODS FOR USE OF THE PEPTIDES AND PEPTIDE DERIVATIVES

The present invention provides methods for modulating the immune response in an individual, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual in an amount sufficient to increase production of at least one Th1 cytokine, such as interleukin 2 and interferon-γ, and/or decrease production of at least one Th2 cytokine, such as interleukin-4, interleukin 5, interleukin 6, interleukin 10, and immunoglobulin G.

In one embodiment, the present invention is directed to methods for increasing production of at least one Th1 cytokine or decreasing production of at least one Th2 cytokine in an individual free of infection with an immunodeficiency-type retrovirus comprising administering an effective amount of a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp

Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual free of infection with an immunodeficiency-type retrovirus in an amount sufficient to increase production of at least one Th1 cytokine or decrease production of at least one Th2 cytokine.

In one embodiment, the present invention provides methods for delaying progression to AIDS, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual infected with an immunodeficiency-type retrovirus in an amount sufficient to delay the progression to AIDS.

The present invention also provides methods for reversing the deleterious effects of infection with an immunodeficiency-type retrovirus, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual infected with an immunodeficiency-type retrovirus in an amount sufficient to reverse the deleterious effects of infection with an immunodeficiency-type retrovirus.

Methods of suppressing progression to immune dysfunction and cytokine dysregulation caused by HIV infection in an individual are also provided by the present invention, said method comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly

Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, in an individual infected with HIV in an amount sufficient to suppress progression to immune dysfunction and cytokine dysregulation.

Moreover, methods of preventing immunosuppression induced by infection with an immunodeficiency-type retrovirus are provided by the present invention, said method comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual infected with an immunodeficiency-type retrovirus in an amount sufficient to prevent immunosuppression.

In yet anther embodiment of the present invention, methods are provided for the prevention and/or treatment of a disease or disorder of the cardiovascular system, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr

Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual in need thereof, in an amount sufficient to prevent or treat a disease or disorder of the cardiovascular system. Illustrative disease and disorders of the cardiovascular system which can be ameliorated, prevented or treated according to the present invention include, but are not limited to, atherosclerosis, arteriosclerosis, atherosclerotic heart disease, reperfusion injury, cardiac arrest, myocardial infarction, thrombus formation, and retrovirus-induced cardiovascular dysfunction.

In yet another embodiment, the present invention is directed to methods for the prevention and/or treatment of an allergic disease or disorder characterized by increased IgE production, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual in need thereof, in an amount sufficient to prevent or

treat an allergic disease or disorder, in which the disease or disorder is characterized by increased IgE production. Illustrative examples of such allergic diseases and disorders characterized by increased IgE production include, but are not limited to, allergy, asthma, delayed hypersensitivity, septic shock, and anaphylactic shock.

In yet another embodiment, the present invention is also directed to methods for inhibiting the growth of a solid tumor or reducing the volume of a solid tumor, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, to an individual having a solid tumor, in an amount sufficient to inhibit the growth of, or reduce the volume of, the solid tumor. Solid tumors include, but are not limited to sarcomas, carcinomas, lymphomas or other solid tumor cancers, such as germ line tumors and tumors of the central nervous system, including, but not limited to, breast cancer, prostate cancer, cervical cancer, uterine cancer, lung cancer, ovarian cancer, testicular cancer, thyroid cancer, astrocytoma, glioma, pancreatic cancer, stomach cancer, liver cancer, colon cancer, and melanoma.

The present invention also provides methods for preventing immunosuppression or suppressing progression to immune dysfunction or cytokine dysregulation in an individual infected with a viral, fungal or bacterial infectious agent other than an immunodeficiency-type retrovirus, comprising administering a peptide selected from the group consisting of peptides comprising the amino acid sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1), Ala Asn Tyr Gly Tyr

Thr Phe Gly Ser Gly Thr Arg Leu Thr Val Val (SEQ ID NO:2), Leu Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:3), Leu Thr Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala (SEQ ID NO:4), Leu Ile Leu Glu Ser Ala Ser Thr Asn Gln Thr Ser Met Tyr Leu Cys Ala (SEQ ID NO:5), Leu Thr Val Ser Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser (SEQ ID NO:6), Leu Ala Ile Ser Gly Leu Glu Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala (SEQ ID NO:7), Phe Thr Ile Ser Gly Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:8), Leu Thr Ile Ser Gly Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln (SEQ ID NO:9), Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser (SEQ ID NO:10) and Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys Gln (SEQ ID NO:11), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Lys Leu Thr Val Val (SEQ ID NO:12), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Glu Leu Thr Val Val (SEQ ID NO:13), Ala Asn Tyr Gly Tyr Thr Phe Gly Ser Gly Thr Asp Leu Thr Val Val (SEQ ID NO:14), and Thr Phe Gly Xaa Gly Thr Yaa, wherein Xaa is any amino acid and Yaa is Arg, Lys, Asp, Glu, His or other charged amino acid molecule (SEQ ID NO:15), or a derivative thereof, in an amount sufficient for preventing immunosuppression or suppressing progression to immune dysfunction or cytokine dysregulation in an individual infected with a viral, fungal or bacterial infectious agent other than an immunodeficiency-type retrovirus.

The individual administered a peptide or peptide derivative of the present invention is an animal, including but not limited to animals such as cows, sheep, pigs, chickens, etc., preferably a mammal, and most preferably a human. Moreover, the individual may or may not be infected with an infectious agent, *e.g.*, viral, fungal, bacterial, which infection results in immune dysfunction or cytokine dysregulation, *e.g.*, infection with an immunodeficiency-type retrovirus.

Various delivery systems are known and can be used to administer a peptide or peptide derivative or a composition comprising a peptide or peptide derivative of the present invention ("Therapeutic"), *e.g.*, encapsulation in liposomes, microparticles, microcapsules, expression by recombinant cells, receptor-mediated endocytosis (see, *e.g.*, Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432), construction of a Therapeutic-encoding nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical

compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention systemically, *e.g.*, via the blood stream. In yet another specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a malignant solid tumor.

In another embodiment, the Therapeutic can be delivered in a vesicle, in particular a liposome (*see* Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; *see* generally *ibid.*)

In yet another embodiment, the Therapeutic can be delivered in a controlled release system. In one embodiment, a pump may be used (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (*see* Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J. Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); *see also* Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J. Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, *i.e.*, the brain, thus requiring only a fraction of the systemic dose (*see, e.g.*, Goodson, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the Therapeutic is a nucleic acid encoding a peptide or peptide derivative of the present invention, the nucleic acid can be administered *in vivo* to promote expression of its encoded peptide or derivative, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, *e.g.*, by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (*e.g.*, a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see *e.g.*, Joliot et al., 1991, Proc. Natl. Acad. Sci. USA 88:1864-1868), etc. Alternatively, a nucleic acid Therapeutic can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a peptide or peptide derivative of the present invention ("Therapeutic"), and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the Therapeutic, preferably in purified

form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The Therapeutics can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The compositions can also contain an adjuvant such as alum, Freund's complete or incomplete adjuvants, poly (AU) or RIBI adjuvant, or coupled to a carrier such as albumin, ovalbumin, or other native or engineered protein.

The present invention also provides for the modification of the peptide or peptide derivative such that it is more stable once administered to an individual, *i.e.*, once administered it has a longer time period of effectiveness as compared to unmodified peptide. Such modifications are well know to those of skill in the art, *e.g.*, polyethylene glycol derivatization (PEGylation), microencapsulation, etc.

The amount of the Therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges, *e.g.*, assays measuring the effect of a Therapeutic on Th1 or Th2 cytokine production in cell culture. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However,

suitable dosage ranges for intravenous administration are generally about 1-1000 micrograms of active compound per kilogram body weight, more preferably about 5-500 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems. Moreover, the compositions can be administered in multiple doses over a period of time.

In one illustrative embodiment, doses of 5 mg/kg of body weight to 25 mg/kg of body weight of the peptide comprising the sequence Cys Lys Pro Ile Ser Gly His Asn Ser Leu Phe Trp Tyr Arg Gln Thr (SEQ ID NO:1) in saline are administered in divided doses following infection with an immunodeficiency-type retrovirus. Preferably, doses of approximately 10 mg/kg of body weight to 25 mg/kg of body weight of the peptide of SEQ ID NO:1 in saline are administered in divided doses. Most preferably, doses of 10 mg/kg of body weight are administered. Multiple doses administered approximately once per month increase the efficacy of the peptide therapy. Dosage amounts, however, may vary depending on the route of administration and depending on whether the peptide is administered with or without adjuvant.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference herein in their entirety.